IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Catherine Castan et al.

Application No.: 10/510,643 Confirmation No.: 1869

Filed: May 23, 2005 Art Unit: 1615

For: ORAL PHARMACEUTICAL FORMULATION IN THE FORM OF AN AQUEOUS SUSPENSION OF MICROCAPSULES FOR THE MODIFIED RELEASE OF ACTIVE PRINCIPLE(S) Examiner: C. E. Helm

DECLARATION OF CATHERINE CASTAN

1. My name is Catherine CASTAN.

2. I have been an employee of Flamel Technologies, S.A. since 1992.

3. My position at Flamel Technologies S.A. is Director of R&D Oral Dosage Forms.

4. I have a Ph.D. in Polymer Chemistry.

5. I have worked in the area of pharmaceutical compositions for 21 years.

6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for modified release of active principles.

7. I reviewed the Office Action that issued on December 7, 2009, for U.S. Application No. 10/510,643.

8. I also reviewed U.S. Patent No. 4,902,513 ("Carvais") and U.S. Patent No. 6,022,562 ("Autant"), references cited by the Examiner in 35 U.S.C. § 103(a) rejections of Application No. 10/510,643.

9. In reviewing the Office Action, it is my understanding that the Examiner is alleging that it would have been obvious to one of ordinary skill in the art to employ coated particles of Autant et al. as the microcapsules in the sustained release, drug saturated suspension of Carvais. *See,* Office Action at page 9.

10. As one of skill in the art, I believe the claimed invention has unexpected and surprising properties because the claimed suspension of microcapsules in an aqueous liquid phase is found to confer the unexpectedly superior claimed release profile upon the microcapsules.

11. At the time of the application, one of ordinary skill in the art would have known that suspensions of microcapsules, including coated microcapsules, suffered from stability problems.

12. While this was known to those of skill in the art, further evidence of this is found in Santus et. al. (EP 0359195, page 2) from 1989 which stated that in the preparation of controlled release liquid pharmaceutical compositions, the "problem is the difficulty of obtaining controlled release liquid preparations apt to maintain for long times the release characteristics of the pharmaceutical substances contained.[…] It may explain why as far as we know, only few controlled release liquid systems are known up to now, and among them, only one is actually commercially available". In 2002, the stability of the release profile in controlled release liquid suspensions was still perceived as a problem difficult enough to explain limited commercial success. See excerpt from the reference textbook by Banks et al., "Modern pharmaceutics, Volume 121", 4th Edition, Informa Health Care, pp. 396-8 (2002). *See* Appendix. Page 397 states: "The formulation of oral sustained-release suspensions has resulted in only limited success due to the difficulty in maintaining the stability of sustained release particles when present in liquid system." As such, it was unexpected for the coated microcapsules of the claimed invention to provide the beneficial stability characteristics as claimed. To the best of my knowledge, less than five controlled release liquid suspension products are commercially available today, indicating that the problem of stability is still current.

13. Page 397 of the Appendix to Banks et al. further states: "Formulation techniques, such as coated beads, drug impregnated wax matrix, microencapsulation, and ion exchange resin, have been used for this purpose". As such, it was unexpected for techniques intended to create sustained release particles, such as those listed on Page 397, to maintain a stability in liquid systems.

14. One of skill in the art would also expect that in a coated microcapsule where the coat contains water soluble materials, the soluble components would dissolve in water.

15. As such, it was unexpected that a microcapsule with a coating containing water soluble materials would maintain coating permeability when placed in an aqueous solution for 10 days.

16. Therefore, one of ordinary skill in the art at the time of the invention would not have foreseen that the claimed coating composition would produce a release profile in an aqueous liquid on day ten similar to the release profile on day zero.

17. Accordingly, Carvais in view of Autant could not teach the unexpected stability of the release profile as claimed: "wherein the *in vitro* release profile of the suspension of microcapsules in an aqueous liquid phase on day ten is similar to the release profile on day zero, as measured using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C".

18. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.

Catherine CASTAN

May 25, 2010

Date

Appendix:
Handbook Banks et al., "Modern pharmaceutics, Volume 121", 4th Edition, Informa Health Care (2002)

the mean free diffusion path of the solute molecules and may thus promote the particle growth.

Polymorphism refers to the different internal crystal structures of a chemically identical compound. Drugs may undergo a change from one metastable polymorphic form to a more stable polymorphic form. Also, the crystal habit might change due to the degree of solvation or hydration. The formation of distinct new crystalline entities during storage is possible. For example, an originally anhydrous drug in a suspension may rapidly or slowly form a hydrate. These various forms may exhibit different solubilities, melting points, and x-ray diffraction patterns. In the preparation of suspensions using precipitation methods, the solvent and the rate of cooling are important factors determining the type of polymorph(s) obtained.

Various drugs are known to exist in different polymorphic forms (e.g., cortisone and prednisolone). The rate of conversion from a metastable into the stable form is an important criteria to be considered with respect to the shelf life of a pharmaceutical product. Polymorphic changes have also been observed during the manufacture of steroid suspensions. When steroid powders are subjected to dry heat sterilization, subsequent rehydration of anhydrous steroid in the presence of an aqueous vehicle results in the formation of large, needle-like crystals. A similar effect may be produced by subject finished suspensions to moist heat sterilization in an autoclave.

Higuchi showed that crystal growth may also arise when the more energetic amorphous or glassy forms of a drug exhibit significantly greater initial solubility in water than their corresponding crystalline forms [84]. In addition, size reduction by crushing and grinding can produce particles whose different surfaces exhibit high or low dissolution rates. This effect can be correlated to differences in the free surface energy introduced during comminution.

To prevent crystal growth and possible changes in particle size distribution, one or more of the following procedures and techniques may be employed [9,89]: (a) selection of particles with a narrow size range; (b) selection of a more stable crystalline form of the drug; (c) avoidance of the use of high-energy milling during particle size reduction; (d) incorporation of a wetting agent (e.g., surfactant) and/or a protective colloid (e.g., cellulose derivatives forming film barriers around the particles); (e) increase of the viscosity of the vehicle to retard particle dissolution and subsequent crystal growth; and (f) avoidance of temperature extremes during storage.

D. Pharmaceutical Suspensions

In the preparation of physically stable pharmaceutical suspensions, a number of formulation components can be incorporated to maintain the solid particles in the dispersed state. These substances can be classified as (a) components of the suspending system, including wetting agents, dispersants or deflocculating agents, flocculating agents, and thickeners, and (b) components of the suspending vehicle (external phase), including pH-control agents and buffers, osmotic agents, coloring/flavoring agents, preservatives, and liquid vehicles. The components of each category are individually selected for their use in the preparation of orally, topically, or parenterally administered suspensions.

Orally administered suspensions containing a wide class of active ingredients (e.g., antibiotics, antacids, radiopaque agents) are of major commercial importance. The solids content of an oral suspension may vary considerably. For example, antibiotic preparations may contain 125–500 mg solid drug per 5 mL or a teaspoonful dose, while a drop concentrate may provide the same amount of drug in only 1–2 mL. Antacid or radiopaque suspensions also contain relatively high amounts of suspended material for oral administration. The suspending vehicle can, for example, be a syrup, sorbitol solution, or gum-thickened water with added artificial sweeteners. Taste and mouthfeel are important considerations when formulating oral suspensions.

Many antibiotic drugs are unstable in the presence of an aqueous vehicle and, therefore, are frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. Generally, this type of product is either a powder mixture or a completely/partially granulated product, which upon dilution and agitation with a specified quantity of vehicle (e.g., water) results in the formation of a suspension suitable for administration [90]. The preparation is typically designated in the USP by a title of the form "For Oral Suspension," whereas the ready-to-use suspension preparations are simply designated as "Oral Suspension." The dry mix products often contain drugs, colorants, flavorants, sweeteners (e.g., sucrose or sodium saccharin), stabilizing agents (e.g., citric acid, sodium citrate), suspending agents (e.g., guar gum, xanthan gum, methylcellulose), and preservatives (e.g., parabens, sodium benzoate).

The formulation of oral sustained-release suspensions has resulted in only limited success due to the difficulty in maintaining the stability of sustainedrelease particles when present in liquid systems. Formulation techniques, such as coated beads, drugimpregnated wax matrix, microencapsulation, and ionexchange resins, have been used for this purpose [91–93]. The combination of an ion-exchange resin complex with particle coating has resulted in a commercial product, the so-called Pennkinetic system. By this technique, ionic drugs are complexed with ionexchange resins, and the drug-resin complex particles are then treated with an impregnating polymer such as polyethylene glycol 4000 followed by coating with a sustaining polymer, such as ethyl cellulose [94,95]. In liquid suspension (the dispersion medium being free of ions that could replace drug ions in the resin complex), the drug remains absorbed to the resin. However, upon swallowing ions from the gastrointestinal liquid can penetrate the particles and replace the drug ions, which subsequently diffuse out of the system (at a controlled, slow rate). Drug release from these systems depends on the type of drug-resin complex, on the ionic environment (e.g., pH and electrolyte concentration within the GI tract), as well as on properties of the resin. Most ion-exchange resins currently employed in sustained-release products contain sulfonic acid groups that exchange cationic drugs possessing amine functionality. An example is hydrocodone polistirex [Tussionex® Pennkinetic Extended-Release Suspension (Pennwalt)].

Topical suspensions are intended to be applied externally. Shake lotion and calamine lotion are good examples of historical products in this class. Because safety and toxicity are dealt with in terms of dermatological acceptability, many useful new suspending agents have been introduced in topical formulations. The protective action and cosmetic properties of topical lotions usually require the use of high concentrations of disperse phase.

In contrast, parenteral suspensions have relatively low solids contents, usually between 0.5 and 5%, with the exception of insoluble forms of penicillin in which concentrations of the antibiotic may exceed 30%. These sterile preparations are designed for intramuscular, intradermal, intralesional, intraarticular, or subcutaneous injection. Syringeability is an important factor to be taken into consideration with injectable dosage forms. The viscosity of a parenteral suspension should be sufficiently low to facilitate injection. Common suspending vehicles include preserved isotonic saline solution or a parenterally acceptable vegetable oil. Ophthalmic and optic suspensions that are sterilized into the eyeleaf must also be prepared in a sterile manner. The vehicles are essentially isotonic and aqueous in composition. The reader should refer to Chapter 12 for further discussion on parenteral products.

E. Methods of Evaluating Suspensions

Suspensions are generally evaluated with respect to their particle size, electrokinetic properties (zeta potential), and rheological characteristics. A detailed discussion on the methods/techniques and relevant instrumentation is given in Sec. VII. A number of evaluating methods done specifically with suspension dosage forms, such as sedimentation volume, redispersibility, and specific gravity measurements, will be treated in this section.

The sedimentation volume of a pharmaceutical suspension can be evaluated using simple, inexpensive, graduated, cylindrical graduates (100–1000 mL). It is defined as the ratio of the equilibrium volume of sediment, V_u, to the total volume of the suspension, V_o.

$$F = \frac{V_u}{V_o} \qquad (12)$$

The value of F ranges between 0 and 1 and increases as the volume of suspension that appears occupied by the sediment increases. For example, if 100 mL of a well-shaken test formulation is placed in a graduate cylinder and the final height of the sediment is at the 20 mL line, then F is 0.2. It is normally found that the greater the value of F, the more stable the product.

When $F=1$, no sediment is apparent and caking is absent, and the suspension is considered esthetically pleasing. This method of evaluation is quite useful in determining the physical stability of suspensions. It can be used to determine the settling rates of flocculated and deflocculated suspensions by making periodic measurements of sedimentation height. Tingstad [86] indicated that a flocculated suspension that settles to a level that is 90% of the initial suspension height ($F=0.9$) and no further is probably satisfactory.

The degree of flocculation, β, is defined as the ratio of the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the suspension when deflocculated, F_∞. It is expressed as:

$$\beta = \frac{F}{F_\infty} \qquad (13)$$